

Screening of cases of acute flaccid paralysis for poliomyelitis eradication: ways to improve specificity*

J.K. Andrus,¹ C. de Quadros,² J.-M. Olivé,³ & H. F. Hull⁴

The Pan American Health Organization in 1985 adopted an initiative to eradicate poliomyelitis from the Western Hemisphere. In 1990, over 2000 cases of acute flaccid paralysis (AFP) were reported in this region, of which <1% were determined to be caused by wild poliovirus. At present, the eradication programme uses AFP as the criterion for surveillance of children aged <15 years; this is 100% sensitive, but not specific. To minimize unnecessary diagnostic investigations, we studied all 4333 cases of AFP reported to the programme during 1989 and 1990 in order to develop more efficient operational screening criteria for cases of AFP.

Among children with AFP, the use of criteria such as age <6 years and either presence of fever at the onset of paralysis or a <4-day period for complete development of paralysis resulted in a sensitivity of 96% (95% C.I. 90–103%) and specificity of 49% (C.I. 47–52%). With criteria of age <6 years and fever present at the onset of paralysis the sensitivity was 75% (C.I. 61–89%) and specificity was 73% (C.I. 71–75%). These results suggest that by screening young children with AFP who either had fever at the onset or showed a rapid progression of paralysis, the number of cases of AFP requiring investigation can be reduced by one half, with minimal compromise in the sensitivity of confirmed poliomyelitis case detection.

Introduction

In September 1985, the Pan American Health Organization officially adopted the initiative to eradicate the transmission of indigenous wild poliovirus transmission from the Region of the Americas (1). In 1986, when aggressive surveillance activities for acute flaccid paralysis (AFP) were first implemented, 930 clinically confirmed poliomyelitis cases were reported in the Americas. By 1988, with improvements in laboratory technology and support, 32 of the 340 cases of AFP confirmed as poliomyelitis were determined to be associated with wild poliovirus isolation (2, 3). Between January and October 1991, six poliomyelitis cases in the Region were found to be associated with wild polio-

virus isolation. This tremendous decrease in the number of confirmed cases occurred despite a doubling in the number of reported cases of acute flaccid paralysis, from 1000 in 1985 to >2000 estimated by the end of 1991.

The challenge to eradicate the transmission of wild poliovirus from the Americas, and ultimately from the world, to a large extent depends on how well we can distinguish "true" poliomyelitis cases, i.e., those caused by wild poliovirus, from cases of AFP due to other causes. Unlike smallpox, which had a characteristic rash of clinical infection and scar of previous vaccination, poliomyelitis has a wide range of clinical presentations that requires skilled examiners and an extensive laboratory support system for diagnosis (4).

Every new case of AFP detected initiates a costly, labour-intensive chain of events that may include containment measures, such as house-to-house immunization campaigns, clinical follow-up to monitor the progression and type of disease, and complex diagnostic laboratory procedures to determine the etiologic agent.^a In 1990, less than 1%

* From EPI/PAHO, Expanded Programme on Immunization, Pan American Health Organization, 525 23rd Street, N.W., Washington DC 20037, USA. Requests for reprints should be sent to this address.

¹ Medical Epidemiologist, EPI/PAHO, on assignment from Centers for Disease Control, Atlanta, GA, USA.

² Senior Regional Adviser, EPI/PAHO.

³ Regional Adviser, EPI/PAHO.

⁴ Medical Epidemiologist, EPI, World Health Organisation, Geneva, Switzerland, on assignment from Centers for Disease Control, Atlanta, GA, USA.

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^a Pan American Health Organization. *Polio eradication field guide*. Technical paper No. 6, 2nd ed. Washington, DC, 1988, pp. 1–53.

of the over 2000 cases of AFP reported were confirmed as caused by wild poliovirus. To minimize inefficient use of the limited resources available for global eradication of poliomyelitis, operational screening criteria that maintain sensitivity, but achieve higher specificity are needed so that case-investigation efforts can focus on the cases most likely to be due to poliovirus.^b To that end, the objective of this study was to develop operational screening criteria which can be applied in the field with more efficient use of the limited global resources.

Methods

Acute flaccid paralysis is a reportable condition in all countries of Latin America. All such cases in children less than 15 years of age that were reported to the Ministries of Health in Latin American countries from January 1989 to December 1990 were enrolled in this study. Information collected from these patients included demographic data, clinical symptoms and signs, and laboratory results. These computerized data are available for analysis in PAHO, Washington, DC.

We compared poliomyelitis cases caused by wild poliovirus (the standard for reference) with all the other cases of AFP. Characteristics more likely to be statistically associated with the former, compared with the latter group, were combined for use as screening criteria. We next compared the two groups for the presence of each screening criterion and calculated their respective sensitivities and specificities.

Patients with AFP were excluded from analysis if information about the relevant symptom or sign had not been recorded or was unknown. Neurological findings on the sensory system and symmetry of paralysis were not analysed. In 1989 and 1990, 55% of the 42 cases caused by wild poliovirus occurred in children aged 1 year or less. Because of the difficulty in performing a sensory examination in children of this age, it was agreed that these findings would not be accurate. As the severity of the paralysis was not indicated, we could not determine the symmetry of paralysis affecting all four limbs, or both upper limbs, or both lower limbs of a child.

Because the objective of the screening criteria analysis was to identify combinations of signs and

symptoms that would guide early interventions and diagnosis at the first patient encounter, we concentrated on clinical findings that present early in the course of the disease; late findings, such as sequelae and atrophy, were therefore not studied as screening criteria. Because less than 40% of the wild virus cases had information on cranial nerve involvement, this variable was also excluded from subsequent analyses.

Before 1990, a case of AFP was confirmed as poliomyelitis if there was (1) laboratory confirmation (wild-type poliovirus isolated from the stool), (2) epidemiological links with another case of AFP or a confirmed case, (3) residual paralysis 60 days after the onset of paralysis, (4) death, or (5) lack of follow-up of a case. Cases were discarded from the study if they did not meet any of these criteria. Beginning in 1990, the designation of confirmed poliomyelitis in the Region of the Americas was changed to those cases of AFP associated with the isolation of wild poliovirus, irrespective of residual paralysis (Table 1) (4).

For the purposes of this study, children with acute flaccid paralysis caused by wild poliovirus were defined as confirmed poliomyelitis cases. Also, for the purposes of this study, "other" categories of poliomyelitis referred to only those polio cases who had died, or had residual paralysis, or were lost to follow-up, but had not been associated with wild

Table 1: New classification of AFP in the Region of the Americas

1. *Confirmed poliomyelitis*: acute paralytic illness associated with the isolation of wild poliovirus, irrespective of residual paralysis.
2. *Vaccine-associated*: acute paralytic illness in which vaccine-like poliovirus is isolated and believed to be the cause of the disease. This category is separate from confirmed poliomyelitis with wild poliovirus isolates.
3. *Poliomyelitis compatible*: acute paralytic illness with compatible residual paralysis at 60 days or followed by death or lost to follow-up, in which at least two adequate stool specimens were not obtained within two weeks of the onset of paralysis for examination in different laboratories.
4. *Not poliomyelitis*: acute paralytic illness in which at least two adequate stool specimens, obtained within two weeks of the onset of paralysis, were negative for poliovirus. Aliquots of the original samples should be held at the laboratory for possible future use. To ensure the accuracy of this designation, any patient who dies, or is lost to follow-up, or has residual paralysis at 60 days should have aliquots of the original specimens examined in two other laboratories in the PAHO network, using all the appropriate techniques. If the specimens were adequate and all were negative, these cases should be considered as "not polio" and "discarded".

^b Andrus, J.K. et al. Classification and characteristics of confirmed polio-cases, the Americas, 1989. In: *Eighth Meeting of the Technical Advisory Group on EPI on the Eradication of Poliomyelitis in the Americas, Mexico City, 19-22 March 1990*. Washington DC, PAHO (document EPI/TAG8/90-10).

poliovirus isolation. Children with acute flaccid paralysis that was not associated with wild poliovirus isolation, or was not determined to be among the other categories of poliomyelitis, or was not vaccine-associated paralysis were designated as "discarded" cases of AFP. These included, but were not limited to, cases of Guillain-Barré syndrome, transverse myelitis, tumours, or trauma.

Sensitivity and specificity, and the confidence intervals around the point estimates were calculated using standard formulae. All other statistical tests were performed using the Epi Info computer software package provided by the Centers for Disease Control, Atlanta, GA, USA.

Results

All 4333 children aged <15 years with AFP who had been reported to the Ministries of Health of their countries in the region of the Americas during 1989 and 1990 were enrolled in the study. In this period, 42 confirmed poliomyelitis cases were reported (Table 2). Although four of the 42 had negative stool isolates, wild polioviruses were isolated from the stools of asymptomatic contacts, so that the index cases of AFP were classified as confirmed poliomyelitis. During the same period, 172 cases were categorized as poliomyelitis (without being associated

Table 2: Classification of AFP cases in the Americas, 1989–90

Category	1989	1990
Wild (confirmed)	24 (19) ^a	18 (17)
Compatible:		
Deaths	18 (14)	13 (12)
Sequelae	59 (46)	41 (39)
Lost to follow-up	20 (16)	21 (20)
Vaccine-associated	7 (5)	13 (12)
Subtotal	128 (100)	106 (100)
Discarded	1802	2297
Total AFP cases	1930	2403

^a Figures in parentheses are percentages.

with wild poliovirus isolation) because they died, or had residual paralysis, or were lost to follow-up. There were no differences between cases in the other poliomyelitis categories (not associated wild poliovirus isolation), whether date of onset of paralysis was in 1989 or in 1990.

A comparison with all other cases of AFP (discarded cases and other categories of poliomyelitis) showed that the predictors of culture-confirmed poliomyelitis cases were an age of less than 6 years and the presence of fever at the onset of paralysis (Table 3). These differences were also detected when

Table 3: Factors associated with confirmed poliomyelitis cases compared to other cases of AFP in the Americas, 1989–90

Factor/organ involved	Confirmed	Other ^a	Odds ratio	P value ^b	m/M ^c
Age <6 years	39 (93) ^d	2443 (58)	9.3	<0.0001	0/2
Females	20 (48)	1864 (44)	0.9	NS ^e	0/1
Prodromal factors:					
Fever	17 (81)	1238 (57)	3.2	0.05	50/49
Respiratory	5 (24)	457 (38)	0.5	NS	50/72
Digestive	12 (60)	863 (41)	2.2	NS	52/63
Meningismus	3 (15)	201 (10)	1.6	NS	52/52
Myalgia	10 (53)	966 (60)	0.8	NS	55/62
Fever at onset	29 (81)	840 (45)	5.1	<0.0001	14/56
<4 days for paralysis to develop	27 (90)	2107 (84)	1.7	NS	29/58
Paralysis of cranial nerve	3 (15)	757 (39)	0.3	0.05	52/54
Sequelae	26 (87)	829 (32)	14.0	<0.0001	29/39
Atrophy	12 (75)	329 (15)	16.8	<0.0001	62/49

^a "Other" = discarded cases + other polio categories not culture-confirmed.

^b By chi-square test.

^c "m" is % of confirmed cases excluded from the analysis and "M" is % of other cases of AFP excluded from analysis, in both instances because of lack of information.

^d Figures in parentheses are percentages.

^e NS = not significant.

the data were analysed by subregion (Mexico; Brazil; Andean countries of Venezuela, Colombia, Ecuador, Peru, and Bolivia; and the Central American countries of Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica, and Panama). Because of the absence of reported confirmed poliomyelitis cases during the study period in the Southern Cone (Paraguay, Uruguay, Argentina, and Chile), this analysis could not be done for this subregion. Clinical features presenting much later in the course of the disease, which were significantly more likely to be associated with disease caused by wild poliovirus than AFP due to other causes, were atrophy and residual paralysis.

Differences between confirmed poliomyelitis and cases of AFP due to other causes did not appear to be solely attributable to differences in the quality of information collected. To control for potential bias in information collection since the confirmed poliomyelitis cases could have more reliable information, the above analyses were repeated on only those children who had at least one stool taken within 29 days after the onset of paralysis. These differences in age, fever at onset, residual paralysis, and the presence of atrophy were confirmed.

When compared to the 172 other categories of poliomyelitis (those who died, had residual paralysis, or were lost to follow-up, but were not associated

with wild poliovirus isolation), the confirmed poliomyelitis cases were more likely to be <6 years (93% vs. 76%, $P = 0.03$) (Table 4). The confirmed cases were also more likely to be younger when compared to each of the subcategories (death, residual paralysis, and lost to follow-up). There were no differences found between the confirmed poliomyelitis cases and cases of vaccine-associated paralysis. Vaccine-associated cases of poliomyelitis and the other categories of poliomyelitis were excluded from subsequent analyses of operational screening criteria.

The early onset characteristics of confirmed poliomyelitis cases (age <6 years, fever at onset of paralysis, and time for the paralysis to develop) were studied in various combinations to determine which would be most useful as a sensitive and specific indicator for screening. Although a period of <4 days for the paralysis to develop completely was not significantly associated with confirmed poliomyelitis cases when compared to AFP due to other causes, this characteristic was present in 90% of the confirmed cases, second only to age >6 years. Therefore, this factor was used as an indicator to maintain as high a sensitivity as possible when analysing the various combinations of criteria.

By definition, the presence of acute flaccid paralysis is 100% sensitive for the identification of paralytic poliomyelitis caused by wild poliovirus but

Table 4: Comparison of confirmed poliomyelitis cases with other categories of poliomyelitis in the Americas, 1989–90

Factor	Confirmed	Other ^a	Odds ratio	P value ^b	m/M ^c
Age <6 years	39 (93) ^d	131 (77)	4.0	0.03	0/1
Females	20 (48)	78 (44)	0.9	NS ^e	0/0
Prodromal factors:					
Fever	17 (81)	86 (76)	1.3	NS	50/34
Respiratory	5 (24)	35 (57)	0.3	NS	50/65
Digestive	12 (60)	53 (50)	1.5	NS	52/38
Meningismus	3 (15)	17 (19)	0.8	NS	52/48
Myalgia	10 (53)	51 (61)	0.7	NS	55/52
Fever at onset	29 (81)	76 (1)	1.7	NS	14/38
<4 days for paralysis to develop	27 (90)	82 (80)	2.3	NS	29/40
Paralysis of cranial nerve	3 (15)	9 (10)	1.5	NS	52/49
Sequelae	26 (87)	104 (96)	0.3	NS	29/37
Atrophy	12 (75)	65 (79)	0.8	NS	62/52

^a "Other" includes poliomyelitis cases who died, or had sequelae or were lost to follow-up.

^b By chi-square test.

^c "m" is % of confirmed cases excluded from the analysis and "M" is % of other cases of poliomyelitis excluded from analysis, in both instances because of lack of information.

^d Figures in parentheses are percentages.

^e NS = not significant.

it is not specific. As expected, increasing the specificity of the operational criteria is associated with a decrease in the sensitivity. While maintaining a sensitivity of 100%, the highest specificity that could be achieved was 34%, when the combination of either fever or both age <6 years and paralysis in <4 days from onset was present. The combination of age <6 years and either fever or paralysis within 4 days resulted in a small drop in sensitivity to 96% (95% C.I. 90–103) and a substantial increase in specificity to 49% (95% C.I. 47–52). Using only age <6 years yielded a sensitivity of 93% (95% C.I. 85–101) and a specificity of 43% (95% C.I. 41–44). The presence of age <6 years and fever at onset of paralysis resulted in a sensitivity of 75% (95% C.I. 61–89) and specificity of 73% (95% C.I. 71–75). The highest specificity (82%, 95% C.I. 80–84) was obtained using the presence of all three variables (age <6 years, fever at onset of paralysis, and a 4-day period for the paralysis to develop completely), but sensitivity dropped to 64% (95% C.I. 47–82).

Discussion

On the basis of these findings, all young children with acute flaccid paralysis who present with fever at the onset of paralysis or whose paralysis rapidly progresses should be investigated without delay so that the diagnosis (using tests including viral culture of stools) can be established and emergency measures can be started to prevent spread of the disease in and beyond the community. In this way, most of the cases of AFP that are not poliomyelitis can be identified and given lower priority for the implementation of appropriate but less costly investigations and control measures. Although it is less sensitive and less specific, the criterion of age <6 years may be considered as an alternative during screening.

These screening criteria, which help to make better use of limited resources when dealing with cases of acute flaccid paralysis, can be applied during the patient's first encounter with the health system. One recent study attempted to develop more specific case definitions for poliomyelitis, which do not necessarily function as screening criteria because of the inclusion of late-onset characteristics.^c Another study used likelihood ratios to predict the

probability that any given case of AFP is caused by wild poliovirus (V. Dietz, unpublished data, 1991). This study, which was limited to only one country, demonstrated that any child with proximal paralysis which developed completely in less than four days, and with fever at the onset of paralysis, was more likely to be confirmed poliomyelitis. To our knowledge, our study is the first to involve data representative of a complete Region.

As regards possible bias in reporting on the presence of fever or the time for paralysis to develop, especially if there is any doubt, the investigator should choose to confirm the patient as poliomyelitis. To eradicate the transmission of wild poliovirus, high sensitivity of any operational screening criteria must be maintained. The choice of what criteria to use, e.g., only age, will depend upon the expertise of field workers in any particular region.

Immunization activities over a period of time may vary worldwide and will diminish the average age of confirmed poliomyelitis cases (5). Those countries just beginning to accelerate immunization activities may have an older age distribution of such cases. However, the presence of fever or the time for paralysis to develop, which are innate disease characteristics, should not vary. Therefore, the screening criterion can be easily modified for any particular area in the world by doing an age distribution analysis of recent cases of poliomyelitis and adjusting the age cut-off in the criteria accordingly.

The screening criteria identified in this study may be more important for field use in countries that are just beginning poliomyelitis eradication activities or still have high incidence rates, e.g., in parts of Africa and Asia. A small drop in sensitivity to gain the specificity needed to reduce the cost for such countries is justified.

Even in the Americas, where poliomyelitis eradication is advanced, these findings have been useful at the central level to monitor the progress of cases of AFP still under investigation. Because it may take up to 10 weeks to receive the final virological results of stool cultures from cases under investigation, the criteria of age <6 years and fever at the onset of paralysis can be used to identify the more critical cases and give them urgent attention.

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^c Bellik, R.-J. et al. Characteristics associated with poliomyelitis case confirmation for use by national eradication programs. In: *Eighth Meeting of the Technical Advisory Group on EPI on the Eradication of Poliomyelitis in the Americas, Mexico City, 19–22 March 1990*. Washington DC, PAHO (document EPI/TAG8/90–12).

Résumé

Dépistage des cas de paralysie flasque aiguë en vue de l'éradication de la poliomyélite: moyens d'améliorer la spécificité

En 1990, moins de 1% des cas de paralysie flasque aiguë (PFA), qui se sont élevés à plus de 2000 dans la Région des Amériques, ont été confirmés comme cas de poliomyélite dus au virus sauvage. Afin d'utiliser au mieux les ressources limitées nécessaires à l'éradication mondiale de la poliomyélite, l'Organisation panaméricaine de la Santé a réalisé une étude en vue d'évaluer l'emploi de critères opérationnels de dépistage qui permettent, tout en préservant la sensibilité, d'obtenir une meilleure spécificité; ainsi, les efforts consacrés à l'étude des cas pourraient être focalisés sur les cas de paralysie flasque aiguë les plus vraisemblablement dus au poliovirus sauvage.

La totalité des 4333 cas concernant des enfants de moins de 15 ans notifiés aux Ministères de la Santé d'Amérique latine de janvier 1989 à décembre 1990 ont été recrutés dans l'étude. On a recueilli pour ces patients des données d'identité, des données démographiques, des informations sur les symptômes cliniques et des données de laboratoire.

Nous avons comparé les cas de poliomyélite dus au poliovirus sauvage avec tous les autres cas de PFA. Les caractéristiques ayant la plus forte probabilité d'être associées de façon statistique avec l'infection par le poliovirus sauvage ont été regroupées pour servir de critères de dépistage. Nous avons comparé dans les deux groupes la présence de chaque critère de dépistage et avons calculé sa sensibilité et sa spécificité.

L'objectif de cette analyse étant d'identifier les associations de symptômes susceptibles d'orienter les interventions et le diagnostic dès la première visite, nous avons surtout cherché les caractéristiques qui apparaissent au début de l'évolution de la maladie.

Lors de la comparaison entre les 42 cas de poliomyélite confirmés par culture et les 4291 autres cas de PFA (cas rejetés et autres catégories de poliomyélite), les facteurs présents dès le début de l'évolution de la maladie et qui permettaient de prédire les cas de poliomyélite confirmés par culture étaient: âge <6 ans (93% contre 58%),

odds ratio [OR] = 9,3, $P < 0,0001$) et fièvre lors de l'installation de la paralysie (81% contre 45%, OR = 5,1, $P < 0,0001$). Bien que non associé de façon significative avec les cas de poliomyélite confirmés, le temps nécessaire à l'installation complète de la paralysie était inférieur à 4 jours dans 90% de ces cas; ce facteur a par conséquent été inclus dans l'analyse ultérieure des critères de dépistage. La seule différence entre les cas de poliomyélite confirmés par culture et les autres catégories de poliomyélite étant l'âge <6 ans, ces autres catégories ont été exclues de l'analyse ultérieure.

L'association âge <6 ans et soit fièvre, soit paralysie installée en moins de 4 jours a entraîné une légère baisse de sensibilité, la faisant passer à 96% (intervalle de confiance à 95% [IC 95%]: 90–103) et une augmentation sensible de la spécificité, qui passe à 49% (IC 95%: 47–52). En utilisant comme seul critère l'âge <6 ans, on obtient une sensibilité de 93% (IC 95%: 85–101) et une spécificité de 43% (IC 95%: 41–44). En prenant comme critère un âge <6 ans et la présence de fièvre au début de la paralysie, on obtient une sensibilité de 75% (IC 95%: 61–89) et une spécificité de 73% (IC 95%: 71–75).

D'après ces résultats, on peut estimer qu'en dépistant les jeunes enfants atteints de PFA qui ont soit de la fièvre au début de la paralysie soit une installation rapide de la paralysie, le nombre de cas de PFA devant faire l'objet d'investigations peut être diminué de moitié, avec des conséquences minimales sur la sensibilité de la détection des cas de poliomyélite confirmés.

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